WE CLAIM:

1. A method of modifying a polypeptide, comprising:

a) identifying at least one immunodominant epitope in a polypeptide using an antibody or population of antibodies obtained from a naïve human or animal or population thereof; and

b) modifying the immunodominant epitope to reduce an immune response to the polypeptide while retaining a substantial therapeutic activity of the polypeptide.

2. A method according to claim 1 wherein the polypeptide is a recombinant polypeptide that has an amino acid sequence that is homologous to all or a part of a native sequence of an endogenous polypeptide in the animal.

3. A method according to claim 1, wherein the polypeptide is a recombinant polypeptide that has an amino acid sequence identical to all or part of a native sequence of an endogenous polypeptide in the animal.

4. The method according to claim 1, wherein the polypeptide is selected from the group consisting of human thrombopoietin, growth hormones, cytokines, receptors, and humanized antibodies.

5. A method according to claim 1, wherein the animal is selected from the group consisting of humans, primates, cattle, pigs, poultry and mice.

6. A method according to claim 1, wherein the modification is a deletion of at least one immunodominant epitope.

7. A method according to claim 1, wherein the modification is a modification of at least one amino acid in the immunodominant epitope by N-glycosylation or pegylation.

8. A method according to claim 1, wherein the modification is a mutation of one or more amino acids in at least one immunodominant epitope.

9. A method according to claim 1, wherein the polypeptide is produced in a non human source.

10. A method of modifying a therapeutic polypeptide, comprising:

a) identifying at least one immunodominant epitope on a therapeutic polypeptide, wherein the immunodominant epitope is identified by binding to antibody or population of antibodies from a naïve human or animal and by binding to an antibody or population of antibodies from an animal or human dosed with the therapeutic polypeptide; and

b) modifying the immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining a substantial therapeutic activity of the therapeutic polypeptide.

11. A method of modifying a therapeutic polypeptide, comprising:

a) identifying at least one epitope on a therapeutic polypeptide, wherein the epitope binds to an antibody or population of antibodies from a naïve human or animal and binds to an antibody or population of antibodies from an animal or human dosed with the therapeutic polypeptide;

b) determining whether the epitope is an immunodominant epitope by using the antibody or population of antibodies from a naïve human or animal and by

using an antibody or population of antibodies from a human or animal dosed with the therapeutic polypeptide; and

c) modifying the immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining a substantial therapeutic activity of the polypeptide.

12. A method of modifying a therapeutic polypeptide, comprising:

a) identifying at least one immunodominant epitope on a therapeutic polypeptide by using an antibody or population of antibodies obtained from a naive human or animal or population thereof, wherein the antibody does not substantially inhibit a therapeutic activity of the therapeutic polypeptide; and

b) modifying the immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining a substantial therapeutic activity of the polypeptide.

13. A method of modifying a therapeutic polypeptide, comprising:

a) identifying at least one immunodominant epitope of a therapeutic polypeptide by using an antibody or population of antibodies from a naive human or animal or population thereof,

b) selecting the immunodominant epitope that is not located in a region of the polypeptide providing a therapeutic activity of the polypeptide; and

c) modifying the selected immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining a substantial therapeutic activity of the therapeutic polypeptide.

14. A method of modifying a therapeutic polypeptide, comprising:

a) identifying at least one immunodominant epitope in a therapeutic polypeptide using an algorithm; and

b) modifying the immunodominant epitope to reduce an immune response to the therapeutic polypeptide while retaining a substantial therapeutic activity of the therapeutic polypeptide.

15. A method according to claim 14, wherein identifying at least one immunodominant epitope comprises:

a) providing a data set of the therapeutic polypeptide;

b) analyzing the data set with an algorithm to identify at least one predicted epitope in the therapeutic polypeptide; and

c) determining whether the predicted epitope is in an immunodominant epitope by immunoreacting a peptide having the sequence of the predicted epitope with an antibody or population of antibodies specific for the therapeutic polypeptide from an animal or a population of animals.

16. A method according to claim 15, wherein the antibodies are from a naïve animal or population of animals.

17. A method according to claim 16, wherein the antibodies do not substantially inhibit a therapeutic activity of the polypeptide.

18. A method according to claim 15, wherein the therapeutic polypeptide is a recombinant polypeptide that is homologous to an endogenous polypetide in the animal.

19. A method according to claim 15, wherein the data set is the linear amino acid sequence of the polypeptide in machine readable form.

20. A method according to claim 14, wherein the algorithm is an algorithm that predicts epitopes that bind to Class II major histocompatability proteins.

21. A method according to claim 14, wherein the algorithm is implemented by a computer.

22. A method for selecting at least one immunodominant epitope to be modified in a polypeptide, comprising:

a) identifying at least one epitope in the polypeptide recognized by an antibody or population of antibodies from a naïve human or animal population thereof and recognized by an antibody or population of antibodies from a human or animal or population thereof dosed with the polypeptide , wherein the polypeptide is homologous to an endogenous polypeptide in the human or animal; and

b) selecting at least one of the identified epitopes by determining whether the identified epitope is in at least one immunodominant epitope in the polypeptide.

23. A modified therapeutic polypeptide having a modification only in an immunodominant epitope, wherein the modification reduces the immune response to the polypeptide while retaining a substantial therapeutic activity of the polypeptide.

24. A modified human recombinant thrombopoietin comprising an amino acid sequence of amino acids 1 to 311 of Figure 7.

25. A modified human recombinant thrombopoietin comprising an amino acid sequence of amino acids 1 to 317 of Figure 7.

26. A modified polypeptide according to claim 23, wherein the polypeptide is human recombinant thrombopoietin with at least one modification of amino acids 312 to 332.

27. A modified polypeptide according to claim 26, wherein the modification is in amino acids 318 to 332.

28. A modified polypeptide according to claim 23, wherein the modification is a deletion, substitution or insertion of at least one amino acid in the immunodominant epitope.

29. A modified polypeptide according to claim 23, wherein the modification is a chemical modification of at least one amino acid in the immunodominant epitope, wherein the chemical modification is N-glycosylation or pegylation.

30. A method of modifying a nucleic acid encoding a modified polypeptide comprising:

a) identifying at least one immunodominant epitope in the polypeptide;

b) providing an isolated nucleic acid sequence encoding the polypeptide; and

c) modifying the isolated nucleic acid to encode a modified polypeptide wherein the modified polypeptide has at least one change in the immunodominant epitope and wherein the change reduces an immune response to the polypeptide while still retaining a substantial therapeutic activity of the polypeptide.

31. The method according to claim 30, further comprising transforming a host cell with the modified isolated nucleic acid.

32. An isolated nucleic acid encoding a modified human thrombopoietin whereby the modified thrombopoietin has a modification only of amino acids 312 to 332.

33. A pharmaceutical composition comprising the modified polypeptide of claim 23 and a pharmaceutically acceptable carrier.

34. A method of treating thrombocytopenia by administering a modified recombinant human thrombopoietin, wherein the human recombinant thrombopoietin has at least one modification only of amino acids 312-332, wherein the modification reduces an immune response to human thrombopoietin while still retaining a substantial therapeutic activity of human thrombopoietin.